with death or rMI). We then validated this model in a pre-specified subgroup of patients from the GRACE registry who met criteria for inclusion in the TIMI 11B trial (n=11505).

**Results:** 8 independent predictors of in-hospital death or rMI found upon presentation were identified (table). The C-statistic for the model was 0.70. Using the model in the TIMI-like subgroup, the C-statistic was 0.70 as well. We also created a simplified, additive scoring system for weighting each predictive variable which can be used to estimate the risk of death or rMI by using a pocket prediction card or handheld PDA.

| | OR (95% CI) |
|---|---|
| Age (per 10 yr increase) | 1.2(1.13 – 1.22) |
| Heart Rate (per 30 bpm increase) | 1.1(1.03 – 1.18) |
| Systolic Blood Pressure (per 20 mmHg decrease) | 1.1(1.04 – 1.15) |
| Initial serum creatinine (per 1 mg/dl increase) | 1.1(1.04 – 1.15) |
| Initial cardiac enzyme elevation | 1.8(1.64 – 2.00) |
| Killip class (per increase in 1 class) | 1.4(1.34 – 1.56) |
| Cardiac arrest at admission | 3.0(2.21 – 3.93) |
| ST segment deviation | 2.1(1.89 – 2.34) |

**Conclusions:**
This GRACE model shows a strong ability to predict the occurrence of the combined endpoint of death or rMI in all patients presenting with ACS and lends itself to incorporation in a handheld PDA or pocket prediction tool for bedside use.



POSTER SESSION

## 1096 Basic Myocardial Infarction

Monday, March 31, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: Noon-1:00 p.m.

### 1096-103 Molecular Basis of Electrical Remodeling in the Infarct Zone

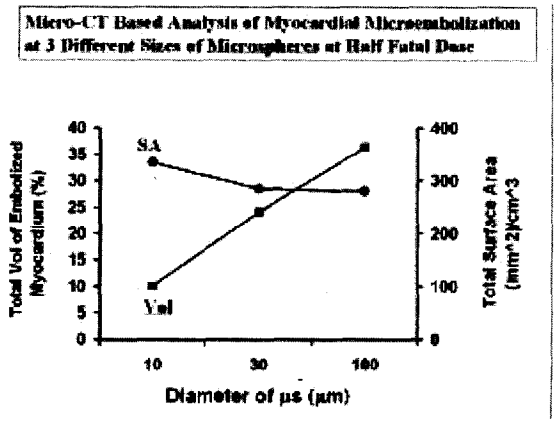
Sumeet S. Chugh, Stacey Whitesel, Srinivasa Nagalla, Oregon Health & Science University, Portland, OR

Background: Altered electrophysiologic properties of infarcted vs non-infarcted myocardium cause reentrant ventricular arrhythmias. A global assessment of comparative differential gene expression would be useful, but has not been performed.
Methods: We therefore, used cDNA microarray gene profiling to characterize differential cardiac gene expression patterns in infarcted vs non-infarcted myocardium of rats (n=9) with surgically induced acute myocardial infarction. LV was harvested and infarcted vs non-infarcted myocardium separated 1, 4 and 5 weeks post-surgery. Total RNA were extracted and pooled for 3 samples at each time point. Fluorescent, labeled complex cDNA probes were generated by reverse transcription and hybridized to microarrays containing 13,824 sequence-verified, non-redundant rodent cDNA clones.
Results: Significant LV infarction was observed in all animals (≥30% LV), with progression to severe dilated cardiomyopathy by 4 wks. Of total genes profiled, n=4, n=42 and n=694 exhibited significant differential expression (Arraystat) in infarcted vs non-infarcted myocardium at 1, 4 and 5 weeks respectively. The earliest differential expression was identified in the T-type voltage-dependent $Ca^{2+}$ channel α 1H subunit (Infarcted 5-fold increase) and mitochondrial $Cl^-$ intracellular channel 4 (Infarcted 5-fold increase). Cell communication, cell growth & maintenance as well as cell death genes exhibited increasing differential expression over time.
Conclusion: Extent of differential gene expression correlated with time period following MI. Early and significant alterations were identified in T-type $Ca^{2+}$ channel and mitochondrial intracellular $Cl^-$ channel.

### 1096-104 Surface Area of Perfusion Defects as the Determinant of the Effect of Coronary Microembolization: A Micro-Computed Tomography Study

Nasser M. Malyar, Mario Goessl, Patricia E. Lund, Erik L. Ritman, Mayo Foundation, Rochester, MN

Background: In Myocardial infarction due to occlusion of an epicardial artery, the impairment of the left ventricular function and clinical outcome is proportional to the volume of infarcted myocardium. As this relationship does not apply in myocardial microembolization (see Figure), we hypothesize that the total surface area of the myocardial microinfarcts is the more important determinant of the clinical outcome.
Materials and Methods: We induced myocardial perfusion defects (MPD) by injecting polymer microspheres (μsph, 10, 30 or 100 μm diameter) at 3 doses (1/8, 1/4 or 1/2 fatal dose) into the LAD or LCX of 8 anesthesized pigs (30 ±1 kg ). 3D micro-CT images, with 20μm on-a-side cubic voxels, were generated of postmortem transmural biopsies (~ 1 cm3) from the embolized myocardium. From these images we calculated the individual and total surface area, and volume, of the embolized territories, for each size and each dose of μsph.
Results: The total volume of the non-perfused territories was logarithmically related to the μsph diameter and the total number of MPD was 203, 145 and 76 for the 10, 30, and 100 μm μsph, respectively. However, the total surface area of the same non-perfused territories was essentially constant, independent of the μsph diameter, as illustrated in the Figure.
Conclusion: The total surface area of the embolized territories is directly related to the fatal impact of myocardial microembolization.




### 1096-105 Mechanical Left Ventricular Unloading Immediately Prior to Reperfusion Reduces Infarct Size

Hela C. Achour, Fernando Boccolandro, Patty Felli, James Amirian, Ricchard W. Smalling, University of Texas Houston Medical School, Houston, TX

Aim- To test the hypothesis that unloading the left ventricle (LV) just prior to reperfusion limits reperfusion related myocardial injury and provides infarct size reduction compared with LV unloading post reperfusion and reperfusion alone. Methods- Twenty-four mongrel dogs were subjected to 2 hours of left anterior descending artery occlusion and 4 hours of reperfusion. A trans-valvular left ventricular assist device (TV LVAD) (Medtronic, Inc) was inserted just prior to reperfusion and maintained during the rest of the experiment in group-1. In group-2 the TV LVAD was inserted and activated just after reperfusion. Group-3 (controls) was subjected to reperfusion alone with no LV support. Pressure catheters were placed in the left atrial appendage, LV apex, and ascending aorta for hemodynamic measurements. Regional myocardial blood flow (RMBF), infarct size, post-reperfusion end diastolic wall thickness (EDWT) in the ischemic region and electron microscopy in the central ischemic zone and control regions were determined. Measurements were made at baseline, 2 hours after coronary occlusion, with reperfusion and at 2, 3 and 4 hours after reperfusion. Results- The hemodynamic data at baseline were similar in the 3 groups. Myocardial infarct size expressed as percentage of area at risk was significantly reduced in group-1 compared to the control group (34.69 ± 4.62% vs 54.58 ± 9.23% respectively, P=0.011) and to group-2 (34.69 ± 4.62% vs 51.51 ± 14.04% respectively, p<0.05). At 4 hours of reperfusion, absolute RMBF in the ischemic zone was slightly higher in group 1 compared to controls, and significantly higher than in group-2 (p=0.04). EDWT tended to return to baseline level in group-1 compared to both controls and group-2, which demonstrated a significant post-reperfusion increase in EDWT and contraction band necrosis in the central ischemic region of these groups. There was a good correlation between the increase in post-reperfusion myocardial wall thickness in the ischemic region and the extent of myocardial infarction. Conclusions- LV unloading prior to, but not after reperfusion, reduces the extent of myocardial injury in canine hearts subjected to 2h of LAD occlusion and 4 hours of reperfusion.

### 1096-106 Nonangiographically Evident Collateral Flow During Primary Percutaneous Transluminal Coronary Angioplasty Favors Contractile Recovery

Anna Sonia Petronio, Ugo Limbruno, Giovanni Amoroso, Roberta Rossini, Marco De Carlo, Andrea Micheli, Luca Pataleo, Caterina Palagi, Paolo Caravelli, Mario Mariani, University of Pisa, Pisa, Italy

BACKGROUND: Recent observations suggest that in patients (pts) undergoing primary PTCA for acute myocardial infarction (AMI), time to treatment has a limited impact on prognosis when greater than 2 hours. Other factors may influence myocardial salvage. The aim of the study was to evaluate if the presence of a preserved and adequate collateral network may limit microvascular damage, and consequently prevent left ventricular dysfunction, during the occlusion of an epicardial coronary artery in pts undergoing primary PTCA with a time to reperfusion > 2 hours.
METHODS: We studied 12 consecutive pts with first uncomplicated AMI, successfully treated with primary PTCA with stenting. All pts had Thrombolysis In Myocardial Infarction (TIMI) grade 0-1 in the infarct-related artery (IRA). Standard abciximab treatment was used in all procedures. Intracoronary pressure measurements were performed immediately before stent implantation in all pts, using a PressureWire System. Collateral flow was assessed as fractional collateral flow (FCF) , determined as the ratio of coronary wedge pressure to mean aortic pressure simultaneously measured during total occlusion of the IRA with an inflated balloon. Changes in echocardiographic wall motion score index (ΔWMSI) and left ventricular end diastolic volume (ΔEDV) were assessed at 4 weeks.
RESULTS: The results of a canonical correlation analysis showed that FCF during AMI was inversely related to ΔWMSI (r=-0.672; p=0.05) and ΔEDV (r=-0.783; p=0.02), but no

correlation was found with time to reperfusion (r=-0.110; p>0.20). A significant correlation was also observed between ΔEDV and peak creatine-kinase (p=0.004; r=-0.849).
CONCLUSIONS: The presence of an adequate, even though non-angiographically evident collateral flow may reduce microvascular damage in the setting of AMI treated with primary PTCA, thus favouring contractile recovery and preventing left ventricular remodeling.

## 1096-107 Rates of Diagnosis of Acute Myocardial Infarction Utilizing Cardiac Troponin-I or Creatine Kinase MB

Joseph C. Lin, Fred S. Apple, MaryAnn M. Murakami, Russell V. Luepker, Hennepin County Medical Center, Minneapolis, MN, University of Minnesota School of Public Health, Minneapolis, MN

**BACKGROUND**: Cardiac troponin-I (cTnI) is a more specific and sensitive biomarker than creatine kinase MB (CK-MB) for detection of myocardial damage. However, the impact of cTnI versus CK-MB on the rates of diagnosis of acute myocardial infarction (AMI) is unclear.
**METHODS**: Seven hundred seventy-six consecutive hospital admissions for suspected acute coronary syndrome (ACS) to an urban acute care hospital over a four month period were analyzed. Patients were aged 18 to 84, residents of the seven-county Twin Cities metropolitan area, and had at least two separate sets of plasma biomarkers sent to the laboratory for evaluation of possible AMI during each hospital admission. cTnI and CK-MB assays (Dade Dimension) were performed concurrently.
**RESULTS**: Using the 10% coefficient of variation (CV) cut-off adopted by the hospital (cTnI > 0.3 ng/mL and CK-MB > 5.0 ng/mL), 116 (14.9%) of the 776 consecutive ACS admissions had positive cTnI. Of these, only 58 (50%) had positive CK-MB. Using a 99th percentile cut-off (cTnI > 0.1 ng/mL and CK-MB > 4.0 ng/mL) instead of the 10% CV cut-off would increase the number of cTnI-positive, CK-MB-negative admissions by 123%. Using the receiver operator characteristic curve-derived cut-off (cTnI > 0.6 ng/mL and CK-MB > 7.0 ng/mL) instead of the 10% CV cut-off would decrease the number of cTnI-positive, CK-MB-negative admissions by 27%.
**CONCLUSION**: Rates of diagnosis of AMI as determined by plasma biomarkers are substantially increased by criteria utilizing cTnI compared to those utilizing CK-MB. Utilizing lower reference cut-offs for these plasma biomarkers markedly increases the rates of cTnI-positive, CK-MB-negative cases.

## 1096-108 Reconstituted High-Density Lipoprotein Restores Endothelial Function in Acute Coronary Syndrome

Remy Chenevard, David Huerlimann, Markus Bechir, Irmgard Andresen, Frank Ruschitzka, Thomas F. Luscher, Georg Noll, University Hospital, Zurich, Switzerland

**Background** Acute Coronary Syndrome (ACS) is associated with severe impairment of endothelial function which correlates well with clinical outcome. Elevated levels of high density lipoprotein have long been recognized as a protective factor in cardiovascular disease. In this study we tested the hypothesis wether reconstituted high density lipoprotein (rHDL) can alter endothelial function in patients diagnosed with ACS.
**Methods** Measurements included (1) venous occlusion plethysmography with acetylcholine (ACH) as an endothelium-dependent vasodilator, nitroglycerine (NG) as direct dilator of vascular smooth muscle cells, results beeing expressed as ml flow per 100 ml tissue; and (2) positron emission tomography (PET) to assess myocardial perfusion at rest and during stress with adenosine, results beeing expressed as ratio of flow under stress/at rest. Experiments were performed before and after infusion of 80 mg rHDL per kg body weight and took place within 7 days after diagnosis of ACS. All patients underwent percutaneous coronary intervention prior to randomization and were on current standard medical treatment.
**Results** 16 patients were included. ACH induced flow increased significantly after infusion of rHDL (6.5 ml/min ±2 to 8.0 ml/min ±2.4, p=0.045). NG-induced blood flow too increased under rHDL as did PET assessed coronary flow reserve (11 ml/min ±2.6 to 14.5 ml/min ±2.7, p=0.03 and 1.2 ±0.1 versus 2.0 ±0.3, p=0.018). Hemodynamic parameters like mean arterial pressure and heart rate remained unchanged (73 mmHg versus 72 mmHg and 64 bpm versus 64 bpm). rHDL infusion was well tolerated in all patients.
**Conclusions** rHDL on top of standard treatment increased vascular reagibility in patients diagnosed with ACS. rHDL possesses pleitropic effects, its anti-inflammatory component may be the most potent as acute inflammation – measured for example as c-reactive protein - is a diagnostic key factor in the outcome of ACS. Despite endothelial function being an excellent surrogate, prospective clinical trials are needed in order to unravel the true potential of rHDL as novel treatment option.

## 1096-109 Abciximab Modulates Apoptosis of Circulating Neutrophils in Patients With Unstable Angina

Antonino Buffon, Annalisa Porto, Giovanna Liuzzo, Antonella D'Annolfo, Donatella Lomaglio, Michela Pinnelli, Antonio G. Rebuzzi, Attilio Maseri, Luigi M. Biasucci, Filippo Crea, Insitute of Cardiology-Catholic University, Rome, Italy

Background. Activated neutrophils have been found in the coronary circulation of unstable angina (UA) patients. Neutrophil apoptosis, a key mechanism to control the intensity of the acute inflammatory response, is markedly reduced in unstable angina (UA) patients. Abciximab modulates neutrophil activation, however its effect on neutrophil apoptosis in UA patients has not been yet investigated. Methods. We investigated spontaneous PMN apoptosis in 6 patients with Braunwald class IIIB UA, in 12 stable angina (SA) patients and 12 healthy subjects. In UA patients, PMN apoptosis was also evaluated 30 min after 0.25 mg/Kg iv bolus of Abciximab. Apoptosis was evaluated by flow cytometry (Annexin V-FITC, Immunotech, Marseille) after PMN isolation from peripheral blood samples (gradient centrifugation, Polymorphprep, Nicomed). Results (median; range). PMN apoptotic rate was significantly lower in UA (18%; 11-34%), than in SA (45%; 6-81%, p=0.02) and healthy subjects (50%; 25-82%, p<0.001). Bolus of Abciximab in UA patients significantly increased neutrophil apoptotic rate (36%; 21-47%, p=0.006 vs baseline); moreover apoptotic rate following abciximab was not different from that observed in SA and healthy subjects. Conclusions. Our study demonstrates that Abciximab increases PMN apoptotic rate in patients with severe UA. Such increased blood clearance of circulating PMN represents a novel anti-inflammatory mechanism of Abciximab.

## 1096-110 A Gene Switch to Amplify the Expression of Multiple Genes Specifically in Cardiomyocytes Under Hypoxia

Yi Tang Keping Qian, Ian M. Phillips, University of Florida, Gainesville, FL

**Background:** One of the challenges for gene therapies is to be able to switch on or off gene expression, ideally by a pathophysiological stimulus. For the purpose of treating myocardial ischemia, we have used hypoxia as the stimulus. Hypoxia-inducible factor 1 α (HIF-1α ) is the master regulator for hypoxia responses. Its protein stability is regulated by its oxygen-dependent degradation (ODD) domain, which triggers a proteosome-mediated degradation only under normoxia. Therefore, we invented an oxygen-sensitive regulator (OSR) as hypoxic gene switch by fusing the ODD domain in between the DNA binding domain of yeast GAL4 and the activation domain of p65.
**Method:** The OSR recognizes and activates a minimal promoter containing GAL4 upstream activating sequences. Three reporter genes, luciferase, β -galactosidase and secreted alkaline phosphatase were inserted downstream of this minimal promoter, respectively. The myosin light chain-2v (MLC-2v) promoter was used to restrict the expression of OSR in the heart. The plasmids were co-transfected into embryonic and adult rat cardiomyocytes and tested under hypoxia (1% $O_2$ or 0.5% $O_2$) and normoxia (20% $O_2$).
**Results:** After transfection, the expression of luciferase was induced under hypoxia 3 to 6 fold in embryonic cardiomyocytes and 16 fold in adult cardiomyocytes. When three different reporter plasmids were co-transfected with OSR, all of them were up-regulated 16 to 18 fold by hypoxia. The OSR could rapidly turn on gene expression with the hypoxic stimulus and turn it off after normal air was restored. Furthermore, the OSR dramatically amplified the power of the MLC-2v promoter up to 300-fold but still maintained its cardiac specificity.
**Conclusion:** The OSR invented in current study is a novel oxygen sensor and gene amplifier, more effective than either HIF-1 or hypoxia response element in switching on and amplifying a cardiac specific promoter. It can be adapted into an adeno-associated virus mediated "vigilant vector" to deliver multiple protective genes to the heart, such as heme oxygenase-1, superoxide dismutase, and VEGF, and simultaneously turn them on in response to ischemia and off in normoxia.

## 1096-111 Can Preinfarction Angina Limit Infarct Size in Patients With a First Q-Wave Myocardial Infarction Undergoing Primary Percutaneous Coronary Angioplasty?

Giuseppe Calveri Carlo N. Dajelli Ermolli, Ylenia Bertelli, Salvatore Caico, Alberto Limido, Jorge A. Uriarte-Salerno, University of Insubria, Varese, Italy

BACKGROUND: In patients with acute myocardial infarction (AMI), preinfarction angina (PA) promotes protective effects in the ischaemic myocardium, reducing the necrosis extension, but its impact in patients treated with primary percutaneous coronary angioplasty with stent deployment (PTST) is not already defined.
METHODS: We studied 183 patients (mean age 66.4 years, 26.8% female), hospitalised in our coronary care unit for a first Q wave AMI and treated with successful primary PTST on the culprit lesion (TIMI3 flow restored). 2D-echocardiographic left ventricular ejection function (LVEF), assessed in the first 24 hours after PTST, was successively compared with LVEF at hospital discharge (after 7-10 days). Myocardial reperfusion was considered successful when at least three of the following criteria were reached (MR-score): (1) early ST-resolution >50% or (2) early T-wave inversion in the first 90 min after PTST, (3) reperfusion ventricular arrhythmias, (4) CK and CK-MB time-to-peak <12 hours. Major Adverse Cardiac Events (MACEs) were evaluated at hospital discharge.
RESULTS: In the study population patients with PA were 75 (mean age 70.1 years 30.7% female). No differences in age, sex or prevalence of coronary risk factors were evidenced. When PA was present, higher mean MR-scores (2.47 vs 1.51 p=0.0420) and successful reperfusion (53.3% vs 36.1% p=0.0207) were reached, especially in association with early T-wave inversion in the first 90 minutes (61.3% vs 41.7% p=0.0089). LVEF on admission was similarly impaired in both PA and non-PA group (39.3% vs 43.6% p=ns) but incidence of early left ventricular expansion was sensibly inferior (1.4% vs 11.1% p=0.0346). At pre-discharge 2D-echo control, per cent improvement of LVEF was demonstrated superior (+26.5% vs +14.8% p=0.0276), while in-hospital MACE was significantly limited (8.0% vs 18.5% p=0.0450).
CONCLUSIONS: Our results suggest that in patients with AMI treated with primary PTST, PA induces protective effects in the ischemic myocardium, probably due to myocyte preconditioning which favours more rapid and effective reperfusion and limits infarct size, improving left ventricular function and in-hospital prognosis.

## 1096-112 Role of Endothelial Nitric Oxide Synthase in Arterial Remodeling in Heart Failure

Mohamed A. Gaballa, Steven Goldman, University of Arizona Sarver Heart Center, Tucson, AZ, Southern Arizona VA Health Care System, Tucson, AZ

To examine the role of nitric oxide (NO) in systemic arterial remodeling in congestive heart failure (CHF) *in vivo*, we measured arterial morphology in the resistance hindlimb vasculature in the rat coronary artery ligation model of CHF 5 days after adenoviral-mediated gene transfer of endothelial nitric oxide synthase (eNOS). The presence of CHF was documented with increases (P<0.05) in left ventricular (LV) end-diastolic pressure, decreases LV systolic pressure, and LV dP/dt. In the resistance vessels, of CHF rats,